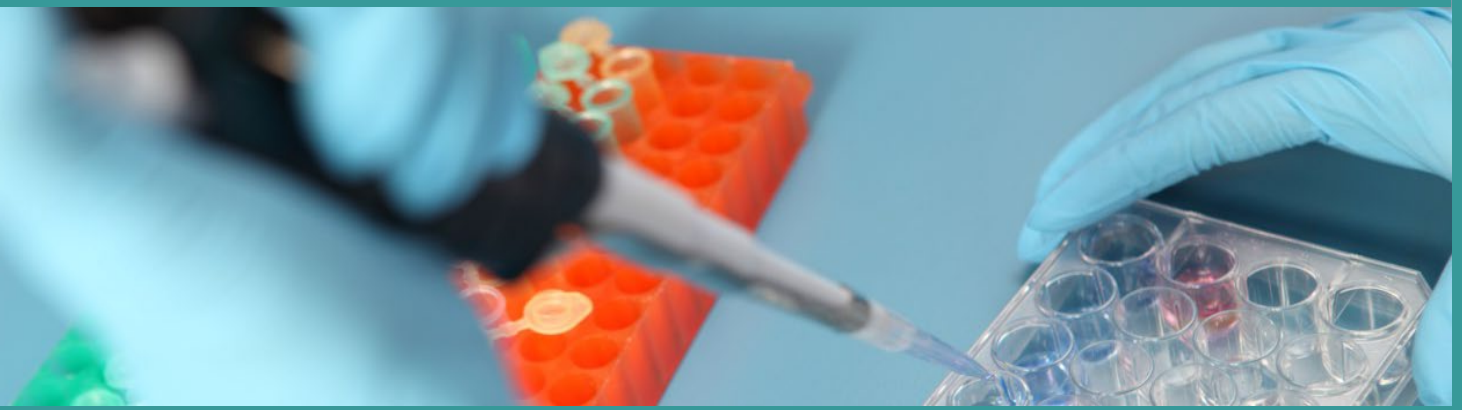
SCANCELL



SCANCELL
AGM presentation

30th October 2018

Dr Cliff Holloway – CEO
Dr Sally Adams – Development Director
Professor Lindy Durrant - CSO

LSE: SCLP.L

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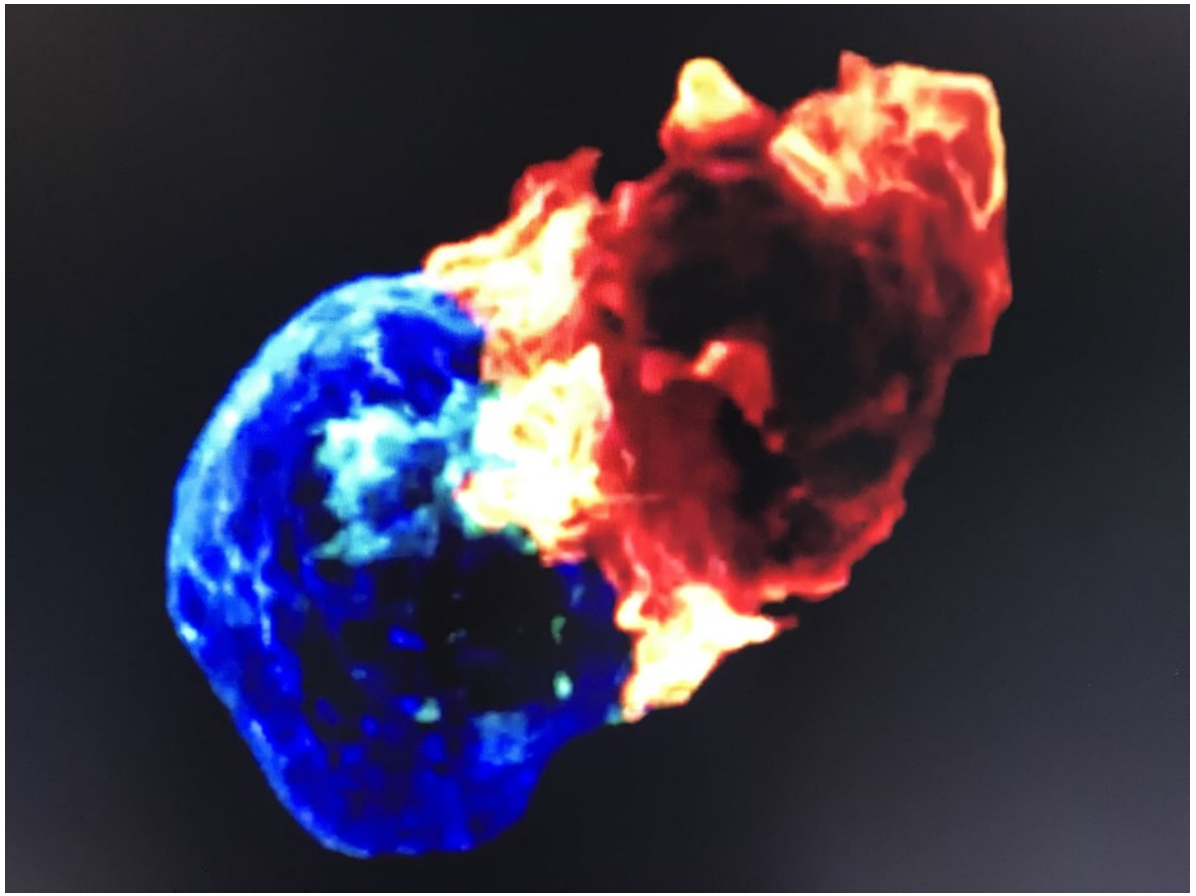
IMMUNOTHERAPY THE '5th PILLAR' IN THE FIGHT AGAINST CANCER

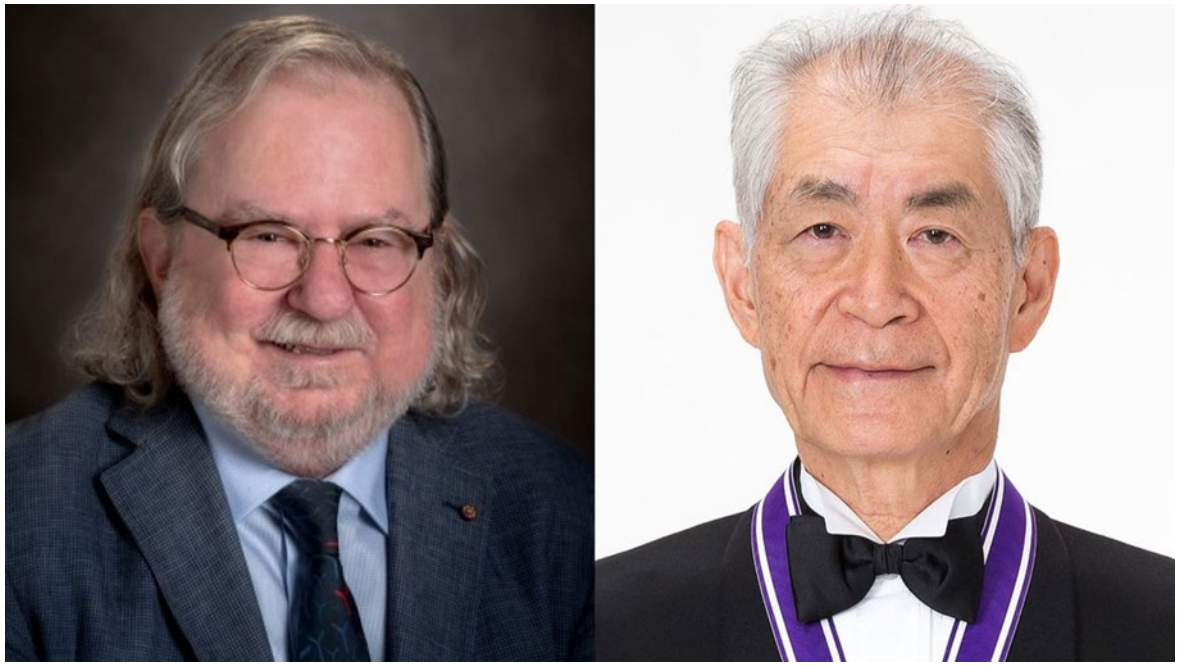
PhRMA
RESEARCH • PROGRESS • HOPE

Cells #GOBOLDLY

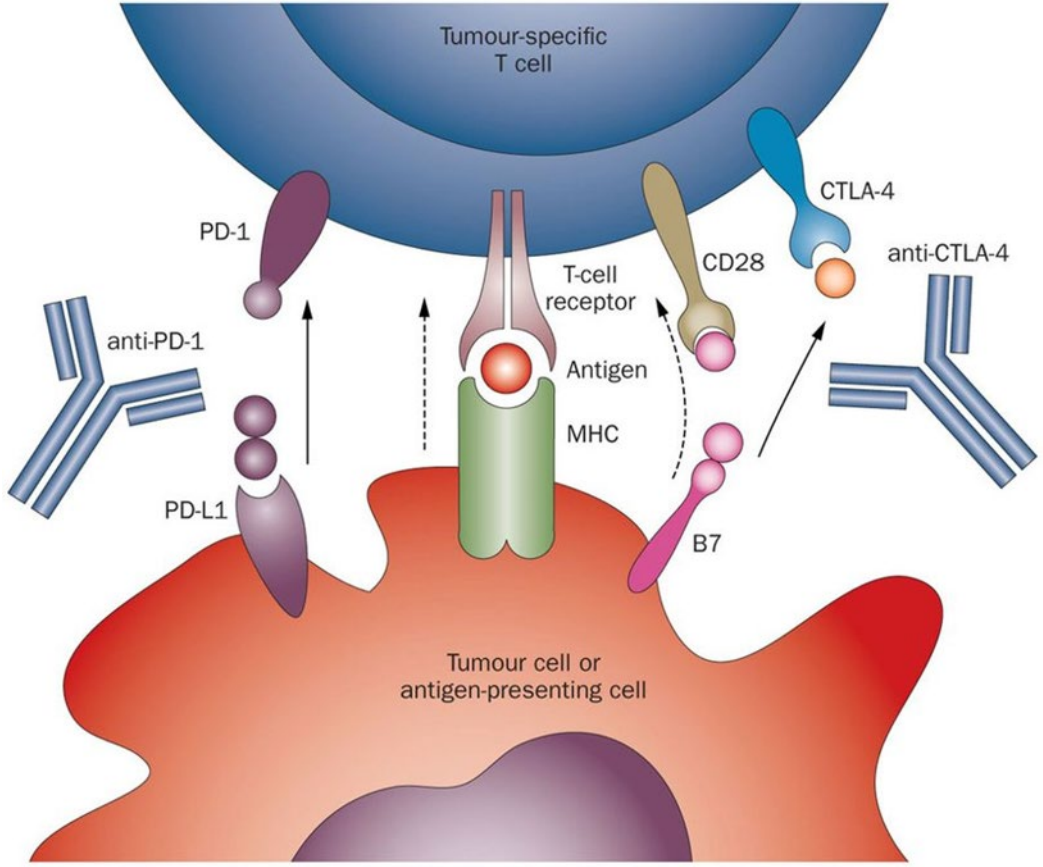


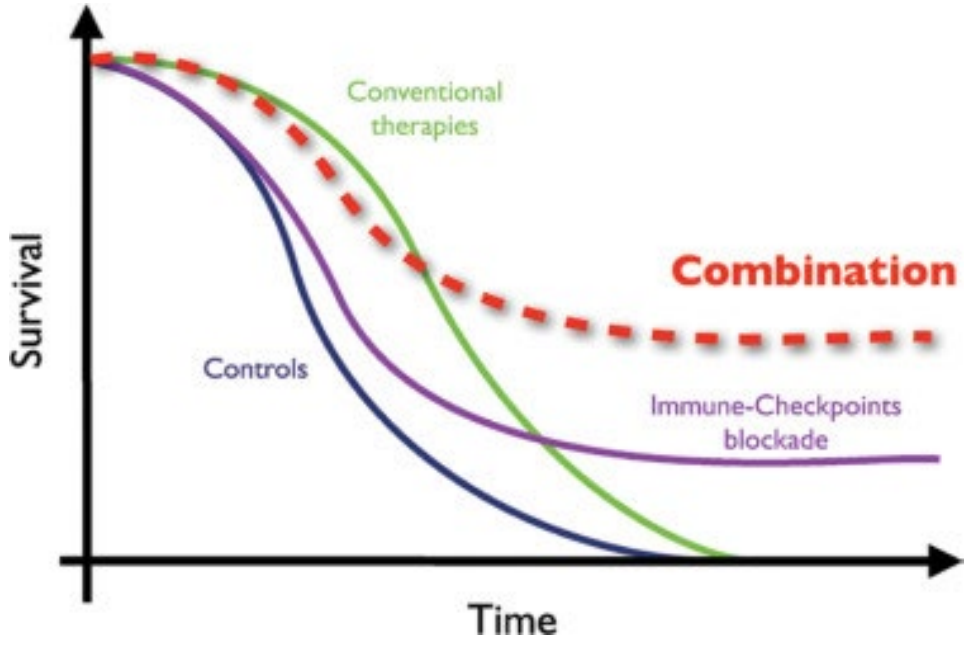
"This is not a video game" - US TV ad showcases the destruction of a cancer cell by immune system

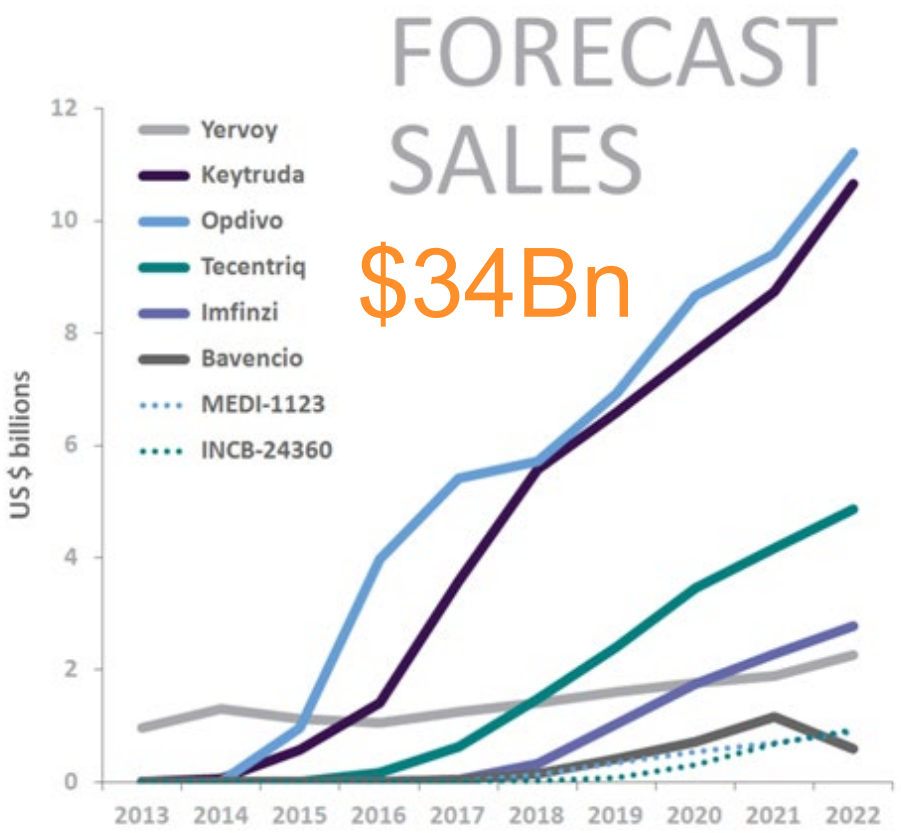
IMMUNE CHECKPOINT BLOCKADE



2018 Nobel Prize in Physiology or Medicine awarded to immunologists James Allison and Tasuku Honjo







Actual sales until 2016; Consensus forecast sales from 2017
(source Thomson Reuters I/B/E/S)

IMMUNOBODY and MODITOPE

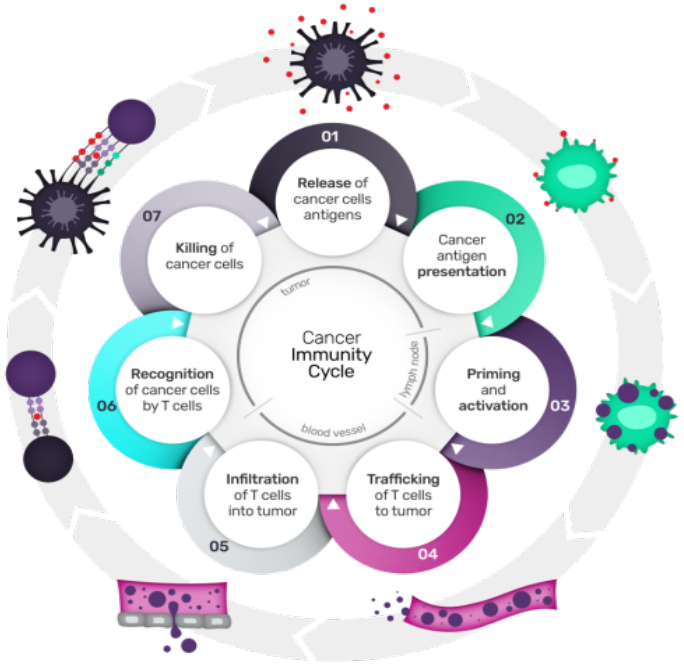
Big Pharma seeking novel drugs or drug-drug combinations that:

- Do not increase toxicity
- Do not significantly increase overall cost of treatment
- Address the unmet needs in hard to treat cancers
- Provide an increased and durable response

Combinations of drugs for better patient outcome driving value in immuno-oncology

MEETING THE NEED FOR EFFECTIVE THERAPEUTIC CANCER VACCINES

- Key challenge is to stimulate an effective T cell response to reject or kill the growing tumour
- Most vaccine strategies only stimulate low frequency, low avidity T cell responses that fail to control tumour growth
- Scancell's novel therapies stimulate **high avidity** CD8 and/or CD4 T-cells that efficiently kill tumours



Ref: Chen and Mellman 2013

TWO DIFFERENTIATED PLATFORMS

IMMUNOBODY®

- DNA-based platform generates high avidity CD8 T-cells by presenting T-cell epitopes of known cancer antigens through a unique dual mode of action

MODITOPE®

- Modified peptides that generate potent killer CD4 T-cells to target antigens induced by stress-induced post-translational modifications (siPTM vaccines)

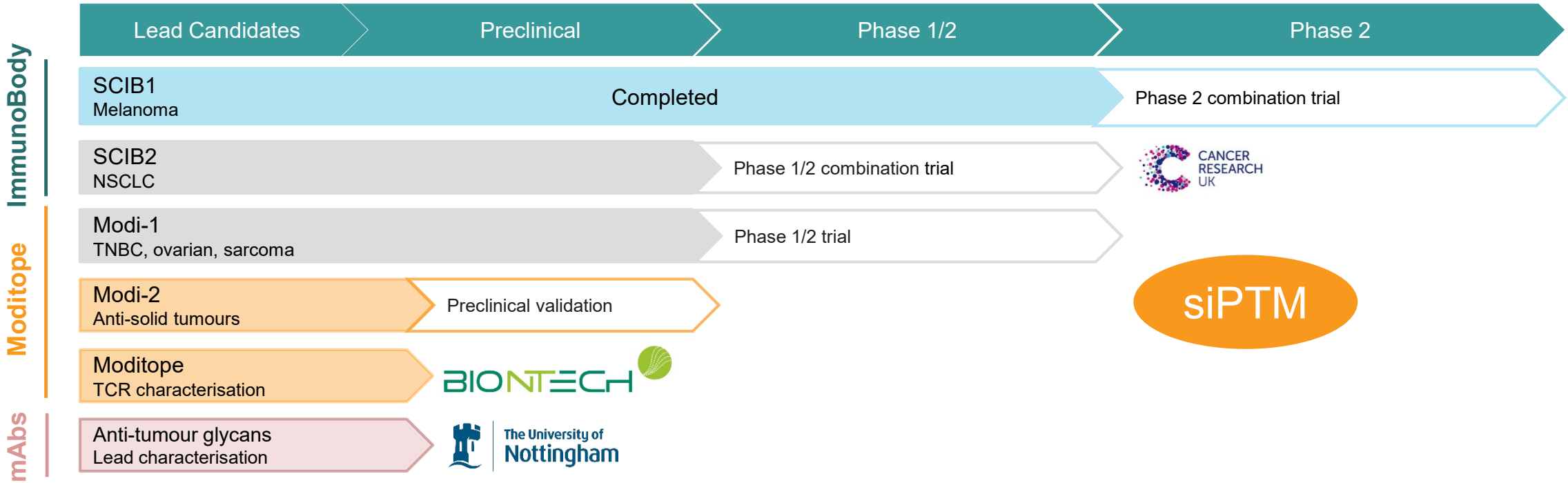
DEVELOPMENT PIPELINE

IMMUNOBODY®

- **SCIB1:** Targets malignant melanoma. Phase 1/2 study completed with strong survival data. Phase 2 combination trial with immune checkpoint inhibitor planned for 1H CY19
- **SCIB2:** Targets NSCLC. Phase 1/2 combination trial with immune checkpoint inhibitor to be funded and sponsored by Cancer Research UK (CRUK).

MODITOPE®

- **Modi-1:** Manufacturing process development initiated. Phase 1/2 trial in TNBC, ovarian and sarcoma planned for 2019.
- **Modi-2:** Targets multiple solid tumours. Preclinical development of selected epitopes.
- **TCR collaboration:** To clone and characterise T cell receptors against Modi-1 specific epitopes.



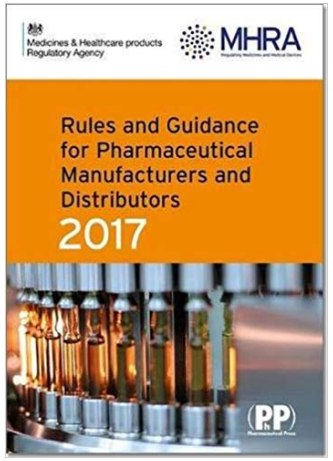
THE DEVELOPMENT PROCESS

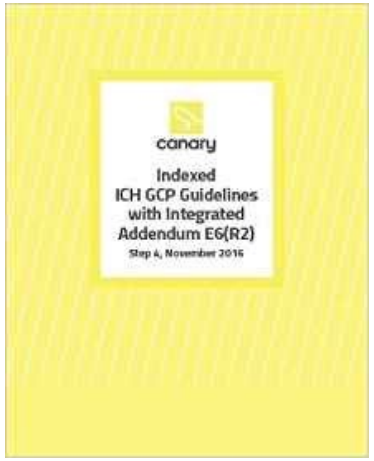
- Can we make it?

- Is it safe?
- Does it make patients better?

COMPLIANCE WITH REGULATORY GUIDANCE

- Good Manufacturing Practice
- Good Clinical Practice
- Good Laboratory Practice





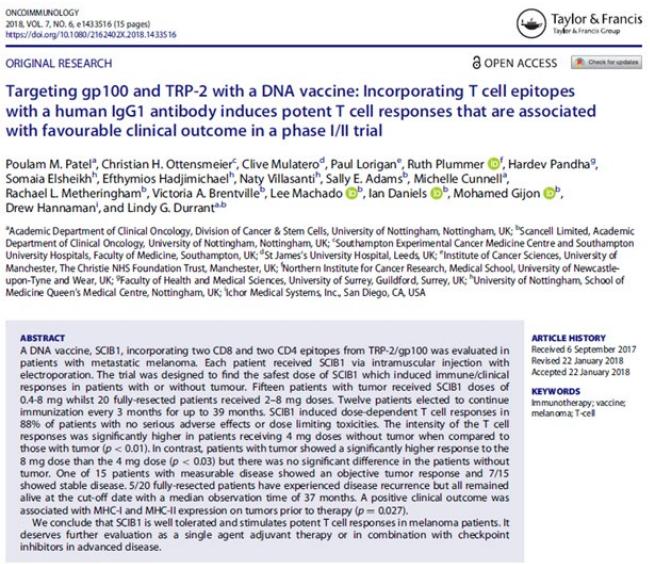
LEGAL REQUIREMENT FOR SPONSOR OVERSIGHT

- Policy documents and procedures
- Standard Operating Procedures (SOP)
- Trial Master File (TMF)
- Investigator Brochure (IB)
- Case Report Forms (CRF)
- Statistical Analysis Plan (SAP)
- Clinical Study Report (CSR)
- Investigational New Drug (IND) application
- Investigational Medicinal Product Dossier (IMPD)

SCIB1

SCIB1 INDUCES POTENT IMMUNE RESPONSES & FAVOURABLE CLINICAL OUTCOME

- Excellent safety profile with no dose-limiting toxicities and **no** serious adverse events related to SCIB1 study drug or Ichor v1.0 delivery device
- Two patients with tumour present at study entry showed regression of lung lesions
- Overall survival with SCIB1 treatment was superior to historical survival rates
- Melanoma recurrence rates were lower in SCIB1-treated patients than historical controls
- Trial data published in OncoImmunology 2018



ONCOIMMUNOLOGY
2018, VOL. 7, NO. 6, e1433516 (15 pages)
https://doi.org/10.1080/2162402X.2018.1433516

Taylor & Francis

ORIGINAL RESEARCH

OPEN ACCESS

Targeting gp100 and TRP-2 with a DNA vaccine: Incorporating T cell epitopes with a human IgG1 antibody induces potent T cell responses that are associated with favourable clinical outcome in a phase I/II trial

Poulam M. Patel[a], Christian H. Ottensmeier[c], Clive Mulatero[d], Paul Lorigan[e], Ruth Plummer[f], Hardev Pandha[g], Somaia Elsheikh[h], Efthymios Hadjimichael[h], Naty Villasanti[h], Sally E. Adams[b], Michelle Cunnell[a], Rachael L. Metheringham[b], Victoria A. Brentville[b], Lee Machado[b], Ian Daniels[b], Mohamed Gijon[b], Drew Hannaman[i], and Lindy G. Durrant[a,b]

[a]Academic Department of Clinical Oncology, Division of Cancer & Stem Cells, University of Nottingham, Nottingham, UK; [b]Scancell Limited, Academic Department of Clinical Oncology, University of Nottingham, Nottingham, UK; [c]Southampton Experimental Cancer Medicine Centre and Southampton University Hospitals, Faculty of Medicine, Southampton, UK; [d]St James's University Hospital, Leeds, UK; [e]Institute of Cancer Sciences, University of Manchester, The Christie NHS Foundation Trust, Manchester, UK; [f]Northern Institute for Cancer Research, Medical School, University of Newcastle-upon-Tyne and Wear, UK; [g]Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey, UK; [h]University of Nottingham, School of Medicine Queen's Medical Centre, Nottingham, UK; [i]Ichor Medical Systems, Inc., San Diego, CA, USA

ABSTRACT

A DNA vaccine, SCIB1, incorporating two CD8 and two CD4 epitopes from TRP-2/gp100 was evaluated in patients with metastatic melanoma. Each patient received SCIB1 via intramuscular injection with electroporation. The trial was designed to find the safest dose of SCIB1 which induced immune/clinical responses in patients with or without tumour. Fifteen patients with tumor received SCIB1 doses of 0.4-8 mg whilst 20 fully-resected patients received 2–8 mg doses. Twelve patients elected to continue immunization every 3 months for up to 39 months. SCIB1 induced dose-dependent T cell responses in 88% of patients with no serious adverse effects or dose limiting toxicities. The intensity of the T cell responses was significantly higher in patients receiving 4 mg doses without tumor when compared to those with tumor ($p < 0.01$). In contrast, patients with tumor showed a significantly higher response to the 8 mg dose than the 4 mg dose ($p < 0.03$) but there was no significant difference in the patients without tumor. One of 15 patients with measurable disease showed an objective tumor response and 7/15 showed stable disease. 5/20 fully-resected patients have experienced disease recurrence but all remained alive at the cut-off date with a median observation time of 37 months. A positive clinical outcome was associated with MHC-I and MHC-II expression on tumors prior to therapy ($p = 0.027$).

We conclude that SCIB1 is well tolerated and stimulates potent T cell responses in melanoma patients. It deserves further evaluation as a single agent adjuvant therapy or in combination with checkpoint inhibitors in advanced disease.

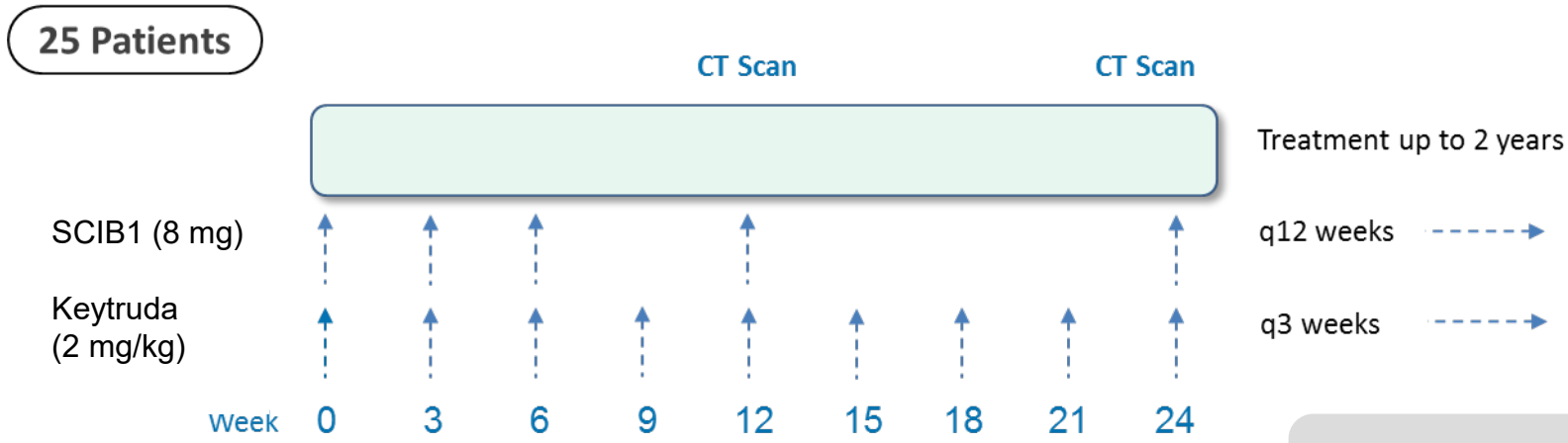
ARTICLE HISTORY
Received 6 September 2017
Revised 22 January 2018
Accepted 22 January 2018

KEYWORDS
Immunotherapy; vaccine; melanoma; T-cell

- Combination of SCIB1 with checkpoint inhibition boosts tumour therapy in melanoma model
- **Rationale for combination trial in humans**

PATIENT POPULATION

- Histologically confirmed, unresectable AJCC stage III or stage IV melanoma
- No prior systemic treatment for advanced disease
- Suitable for treatment with Keytruda (pembrolizumab), with measurable disease
- Part 1 safety run-in (n=6); Part 2 additional 19 patients; total = 25 patients



Trigger to advance development ≥ 12 RECIST responses in 25 patients

Assumptions

- Response rate to Keytruda = 30%
- Response rate of interest for combination = 55%

- International trial to be conducted under an Investigational New Drug (IND) application
  - Up to 5 sites in US and UK
- New TDS-IM v2.0 electroporation device, designed to support eventual commercial deployment

- US regulatory submissions
  - IND for study drug SCIB1 manufacturing, preclinical pharmacology, toxicology, previous experience in human submitted to CBER (Center for Biologics Evaluation and Research)
  - Master File for TDS-IM v2.0 device submitted to CDRH by Ichor (Center for Devices and Radiological Health)
- UK regulatory submissions
  - MHRA clinical trials division for drug safety
  - MHRA devices division for TDS-IM device safety
  - HRA – Health Research Authority for ethics and site approvals

SCIB1 IND SUBMISSION

CSR = 2,688 pages

Form 1571

IND application

RECORDS

Research reports, toxicology reports, manufacturing batch records, raw materials CoAs, SOPs, QC analysis, compliance reports, analytical validation reports, release documents, environmental monitoring reports, cleaning validation reports, process validation reports, stability reports, references, drug labelling, SCIB1-001 clinical study report, specifications, protocol, patient information sheet, informed consent form, Investigator Brochure

SCIB1 IND REVIEW PROCESS

- IND submitted ✓
- Reviewed by FDA
  - SCIB1 clinical and toxicology questions answered during review process ✓
  - CMC questions under control ✓
- Deficiencies in cross-referenced Ichor TriGrid v2.0 device Master File
  - Device-specific questions
  - Responses being prepared by Ichor in consultation with Scancell
- Complete response required for review by FDA
- Continue to plan for study start in UK and US, subject to regulatory approval ✓

CORE CLINICAL TRIAL MANAGEMENT ACTIVITIES

Project/Study Management

- Protocol development
- Contracts
- Partnership management
- Finance
- Study oversight

Regulatory & Ethics

- Protocol submission
- Safety reporting
- Annual updates

Clinical Monitoring & Supplies

- Site selection
- On-site and remote monitoring
- Site management
- Sample management
- Study materials

Medical Monitoring & Safety

- Therapeutic training
- Medical advice
- Safety oversight

Biometrics

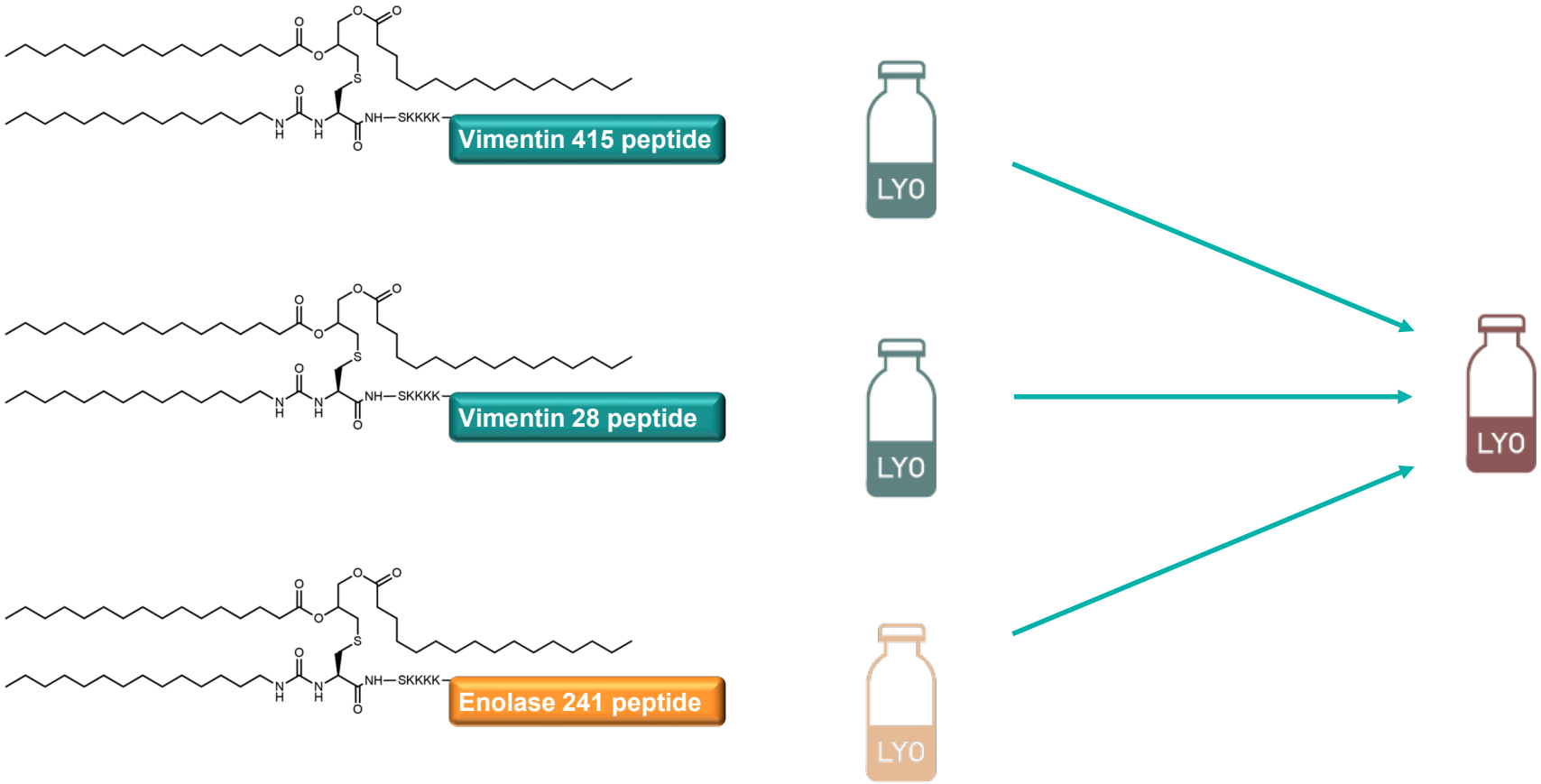
- Electronic data capture
- Data management
- Biostatistics
- Medical writing

SCIB1 DEVELOPMENT

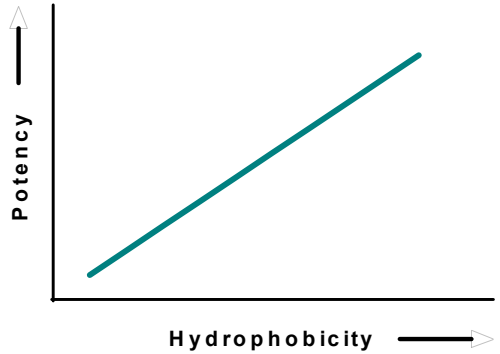
- IND submitted
- SCIB1-specific questions under control
- Device-specific questions in hand
- Operational activities underway
- UK regulatory submissions in progress
- Trial ready to start as soon as approval received

MODI-1

THREE DRUG SUBSTANCES = ONE DRUG PRODUCT



- Modi-1 conjugates - novel cutting-edge products
- Strong bias toward hydrophobic amino acids at T-cell receptor contact residues within immunogenic epitopes (Chowell *et al* 2015)
- Hydrophobic peptides
  - Challenging synthetic properties
  - Manufacturing
  - Analytical development

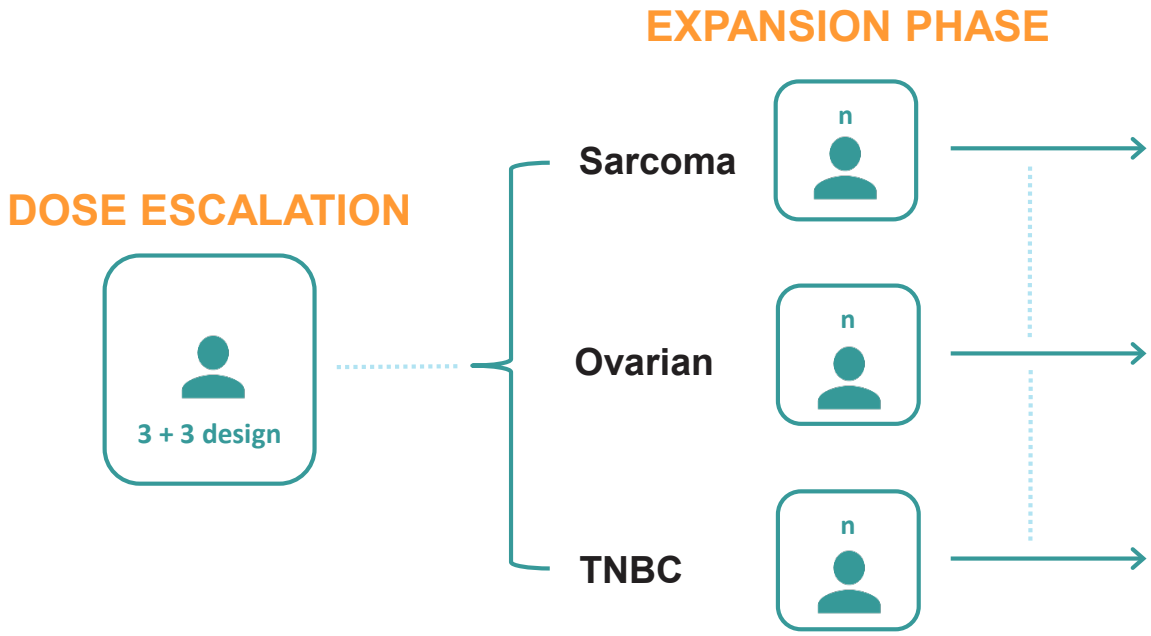


- Polypeptide Group (PPL) selected as GMP manufacturer
  - World leader in synthesis of complex peptides
  - Process defined for all three conjugates

PolyPeptide GROUP

PATIENT POPULATION

- Patients with tumours with high vimentin or enolase expression (e.g., sarcoma, triple negative breast cancer, ovarian)
- Failed or intolerant to standard of care therapies



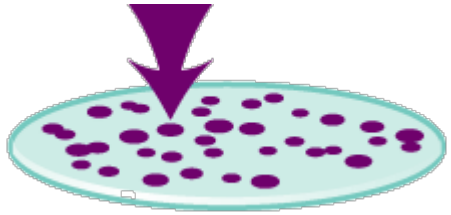
Dosing regime

Dose escalation: 10, 50, 250 µg
Weeks 1, 3, 6, 12 and 24
Patients may continue to receive Modi-1 at 12-week intervals up to 2 years

FROM RESEARCH TO DEVELOPMENT…

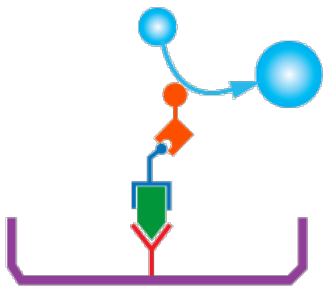
Does it work?

New idea!



Can we measure it?

Can we make it?

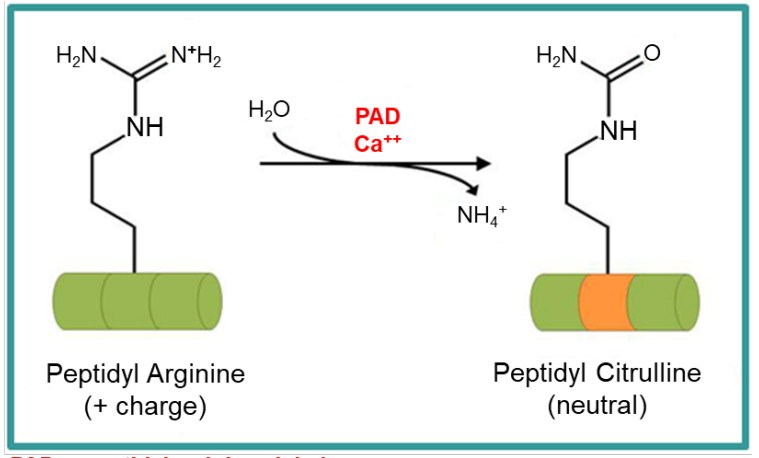


Is it safe?

MODI-2

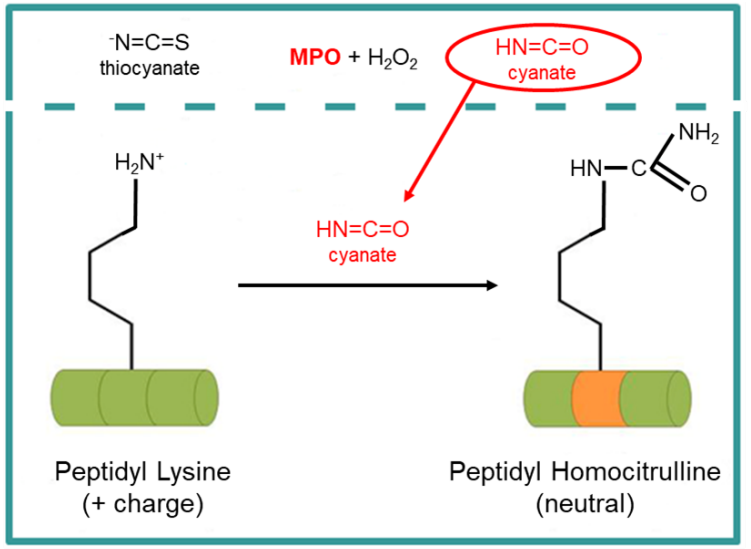
THE MODITOPE® PLATFORM

- One such modification involves the process of **CITRULLINATION**
  - The alteration of proteins due to enzymatic conversion of arginine residues to citrulline
  - Citrullination occurs as a result of a degradation and 'recycling' process called **autophagy** that is induced in stressed cells, including cancer cells
  - Citrullinated epitopes presented on **MHC class II**
  - Patent awarded in Europe, Japan, China, Australia; still being pursued in US but attorney confident we will get broad claims



PAD = peptidylarginine deiminase

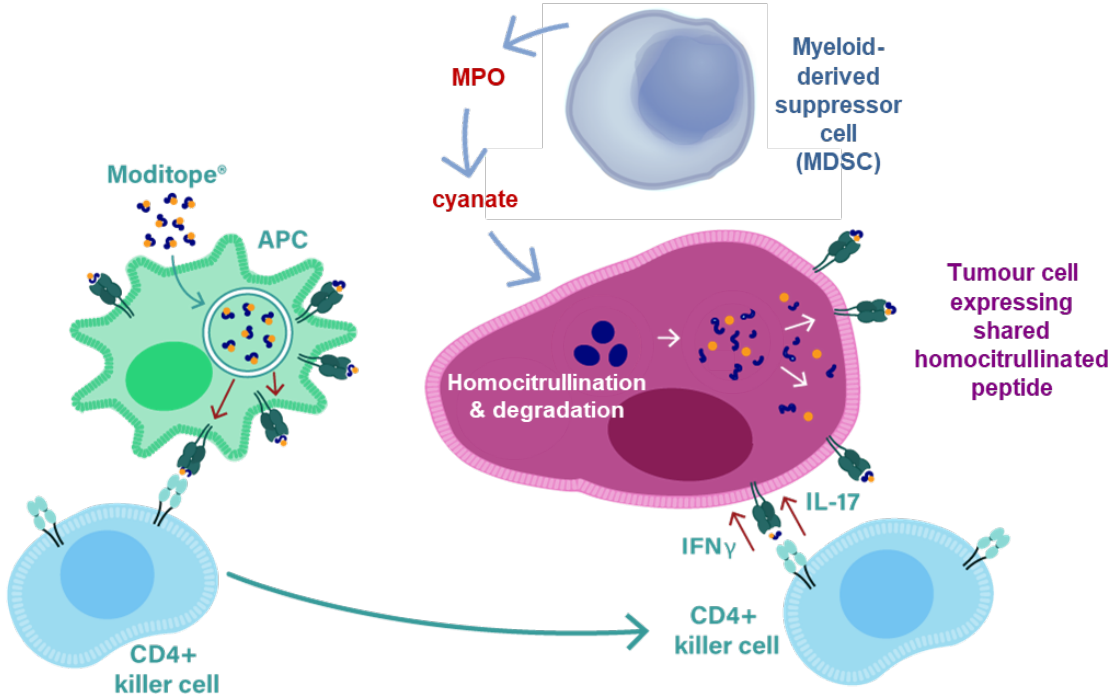
- Another modification involves the process of **HOMOCITRULLINATION**
  - The alteration of proteins due to conversion of lysine residues to homocitrulline
  - Homocitrullination occurs as a result of MPO released by myeloid-derived suppressor cells (MDSC) which converts thiocyanate to cyanate in the presence of H_2O_2
  - Cyanate diffuses into tumour cells and results in spontaneous homocitrullination of cytoplasmic proteins
  - These proteins are degraded during **autophagy** and homocitrullinated epitopes presented on **MHC class II**
  - Patent filed with broad claims in cancer and composition of matter for any use of homocitrullinated peptides



MPO = myeloperoxidase

HOMOCITRULLINATED PEPTIDES ACTIVATE T-HELPER CELLS THAT SEEK AND DESTROY CANCER CELLS

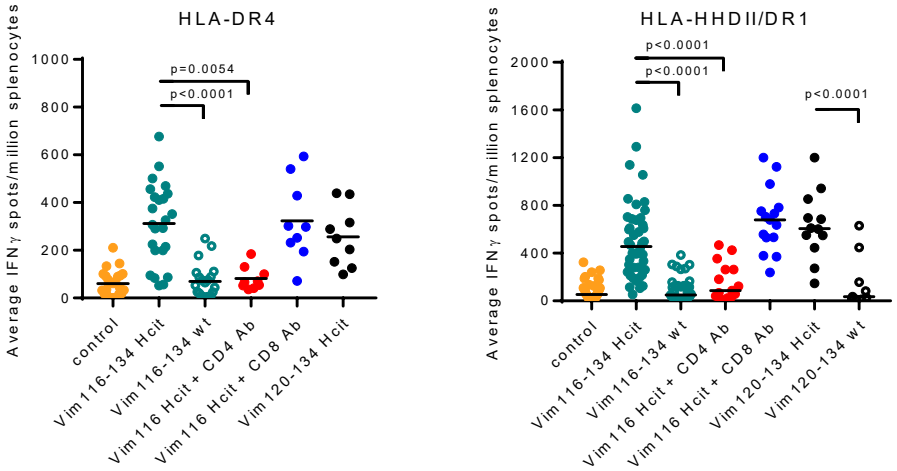
- Homocitrullinated tumour-associated peptides (Moditope peptides) are administered with adjuvant to activate antigen presenting cells (APCs)
- Moditope peptides are taken up by activated APCs
- APCs present peptides to CD4 killer T-cells
- Primed CD4 killer T-cells enter the circulation
- Tumours contain many MDSCs to prevent immune attack
- MDSCs produce MPO which catalyses the production of cyanate resulting in homocitrullination of cytoplasmic proteins within tumours
- CD4 T cells release IFNγ at the tumour site and induce expression of MHC class II molecules presenting the homocitrullinated epitopes
- Primed CD4 killer T-cells destroy cancer cells



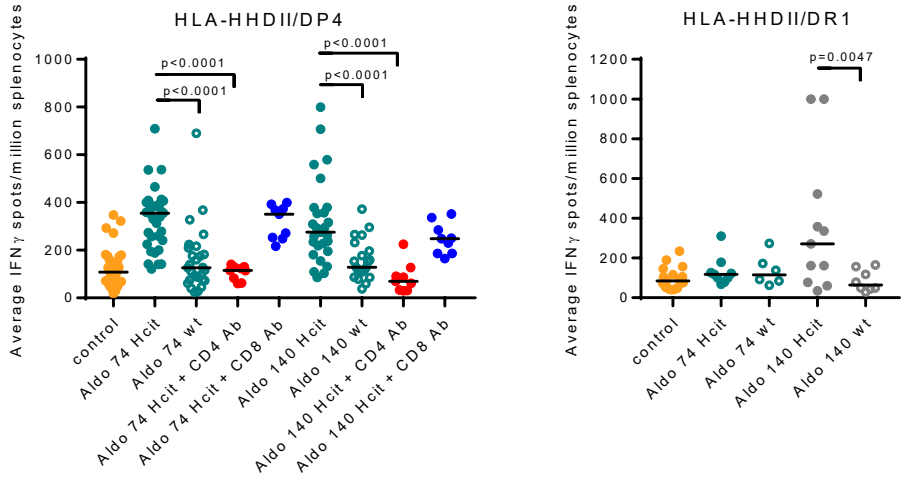
T CELL RESPONSES TO HOMOCITRULLINATED VIMENTIN & ALDOLASE

- Vimentin 116 Hcit - DR4, DR1
- Aldolase 74 Hcit - DP4
- Adolase 140 Hcit - DP4
- Responses are blocked by anti-CD4 mabs

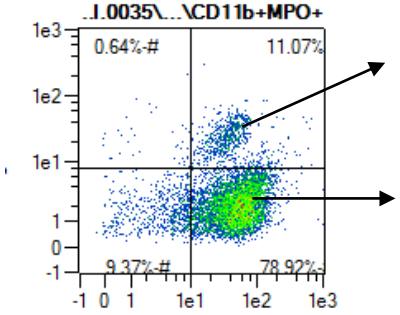
VIMENTIN



ALDOLASE



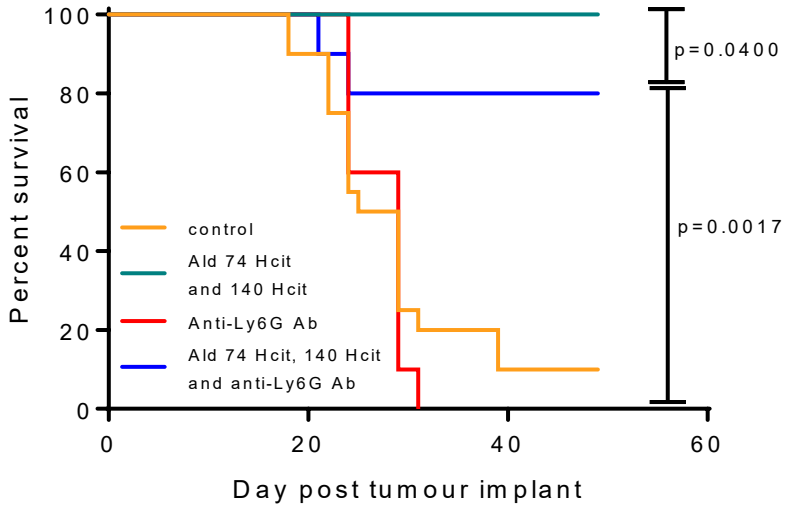
DEPLETING Ly6G+ AND Ly6C+ CELLS REDUCES ANTI-TUMOUR RESPONSE

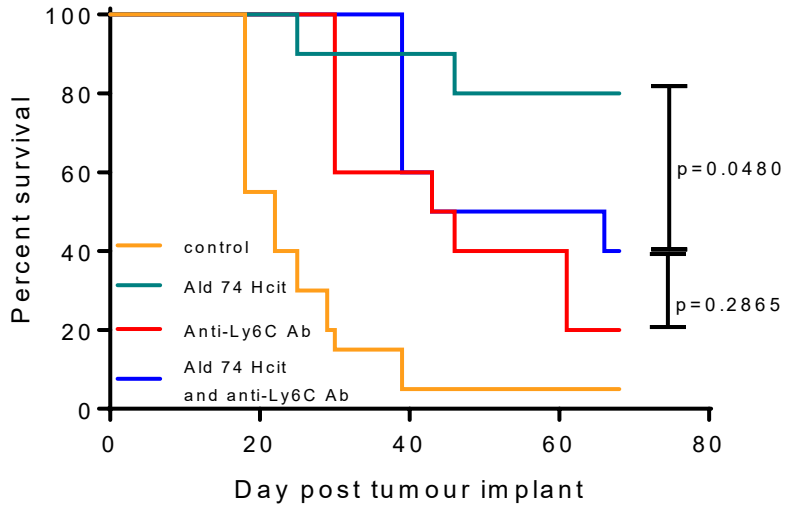


CD11b+ Ly6G+ Ly6C^{lo} = granulocytic MDSC

CD11b+ Ly6G- Ly6C^{hi} = monocytic MDSC

- Antibodies which deplete MDSC abrogate the anti-tumour response to homocitrullinated peptides
- Ly6C+ cells are more potent than Ly6G+ cells





USING PREDICTION ALGORITHMS TO SELECT EPITOPES

- IEDB prediction

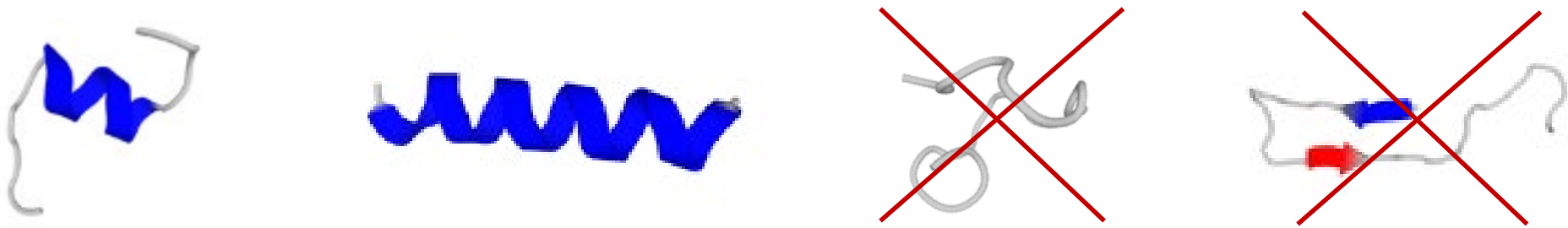
  http://www.iedb.org/

  - High predicted binding to HLA alleles
  - Peptides that contained lysine residues within the predicted binding core

- PEP-FOLD3

  http://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py#forms::PEP-FOLD3

  - Peptides which generate T cell responses have a spiral conformational structure
  - Defined as containing 5 or more amino acids that spiral



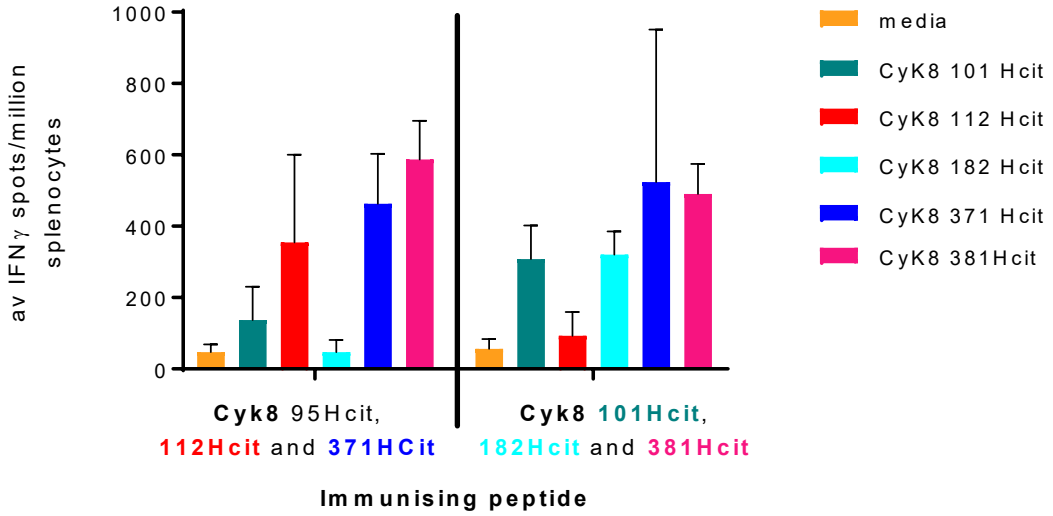
EXAMPLE: CYTOKERATIN 8

Co-ordinates	Sequence	DP4 prediction score	DP4 predicted cores	DR4 prediction score	DR4 predicted cores	DR1 prediction scores	DR1 predicted cores	Spiral	T cell response
101-120	KFASFID-Hcit-VRFLEQQN-Hcit-MLE	0.97 – 17.18 0.97 – 1.68 6.08	IDKVRFLEQ SFIDKVRFL FIDKVRFLE	5.06 25.16 – 37.08 25.16 – 26.26 5.06 – 37.08	FLEQQNKML IDKVRFLEQ FASFIDKVR VRFLEQQNK	12.27 12.27 – 66.46 63.29 65.16	FLEQQNKML VRFLEQQNK FASFIDKVR KVRFLEQQN		Yes
112-131	LEQQN-hcit-MLET-hcit-WSLLQQQ-hcit-T	3.16 – 4.72 3.16 – 4.72	KMLETKWSL MLETKWSLL	12.19 – 24.67 12.19 – 15.38 12.96 – 15.38 24.67	MLETKWSLL LETKWSLLQ KMLETKWSL QNKMLETKW	31.04 – 44.89 44.89 – 46.47 31.04 – 44.89	KWSLLQQQK MLETKWSLL LETKWSLLQ		Yes
182-202	EIN-hcit-RTEMENEFVLI-hcit-hcit-DVDE			27.44 – 41.36 36.01 – 41.15 33.01	MENEFVLIK FVLIKKDVD INKRTEMEN	69.5 – 75.9	MENEFVLIK		Yes
371-388	LREYQELMNV-hcit-LALDIEI	24.36 – 26.69 24.36 – 26.69	LMNVKLALD ELMNVKLAL	4.42 – 5.8 5.76	YQELMNVKL LMNVKLALD	6.74 – 20.92 6.74 – 20.92	YQELMNVKL ELMNVKLAL		Yes
381-399	hcit-LALDIEIATYR-hcit-LLEGEE	18.10 – 24.62 24.62	IEIATYRKL IATYRKLLE	12.39 – 27.03 23.47 – 27.68 27.68	LDIEIATYR IATYRKLLE YRKLLEGEE	39.89 – 27.66	IEIATYRKL		yes

T-CELL RESPONSES TO Cyk8 EPITOPES SELECTED USING ALGORITHMS

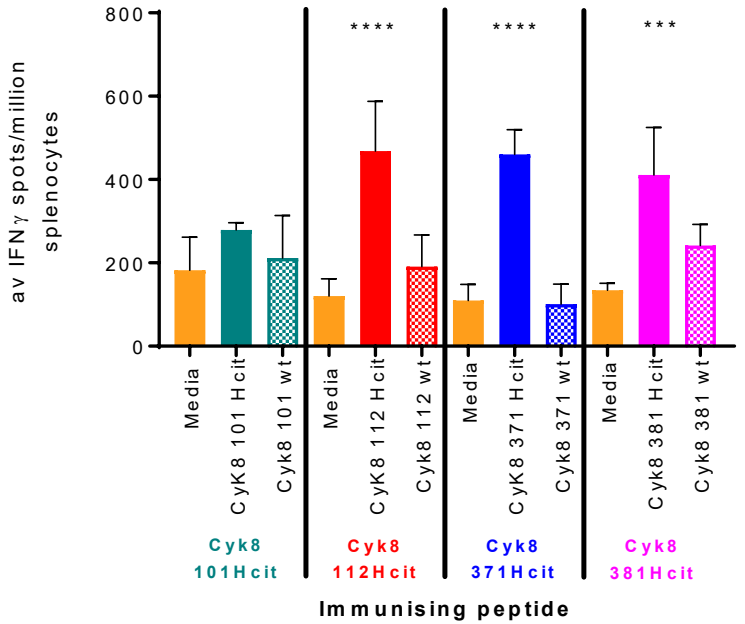
INITIAL SCREEN (HHDII/DR1)

All 5 peptides showed good responses when administered as a pool



RE-SCREEN (HHDII/DR1)

Responses that have been re-screened as homocitrulline-specific



A NEW STRESS-INDUCED POST-TRANSLATIONAL MODIFICATION (siPTM)

- Homocitrulline is a new modification that is an excellent target for tumour immunotherapy
- Strong patent protection
- Targets a different range of cancers to citrullination (Modi-1)
- Different mechanism of action – tumours with a very immunosuppressive environment
- Could target tumours in the event of escape from citrullinated Moditope® vaccines

MODITOPE® PROVIDES A NOVEL PATHWAY FOR CD4-BASED TCR THERAPY

ADVANTAGES

- Moditope® targets epitopes recognised in the context of MHC class II/cytotoxic CD4 T cells
- Recognises widely expressed modified antigens on widely expressed MHC, so has broad utility against a wide range of cancers

MODI-1 (citrullinated epitopes)

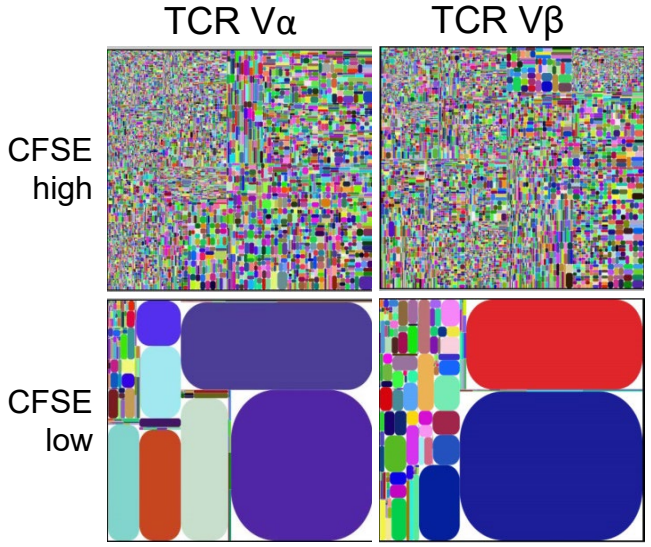
- Research collaboration with BioNtech announced January 2018

MODI-2 (homocitrullinated epitopes)

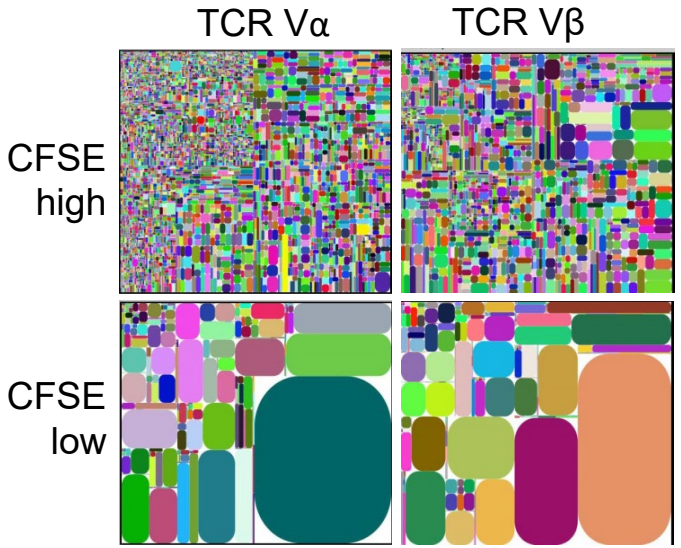
- New modification platform available for TCR research & development

RESPONSES IN HEALTHY DONORS SHOW AN OLIGOCLONAL RESPONSE TO CITRULLINATED PEPTIDES

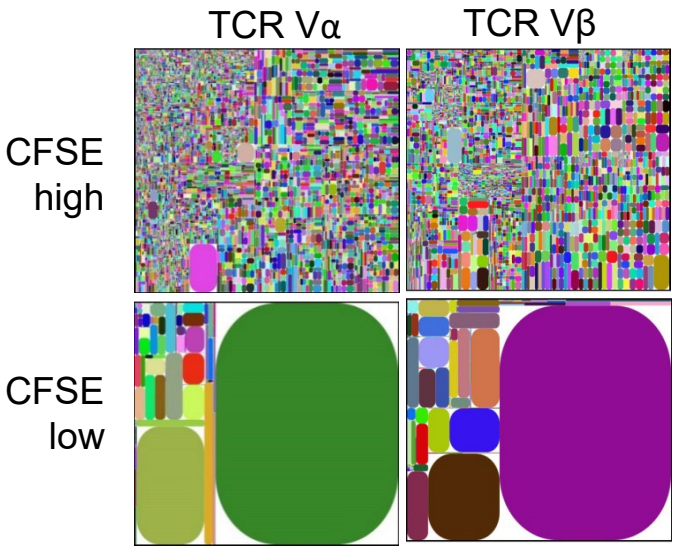
Vim28cit (BD0011)



Vim415cit (BD0008)



Eno241cit (BD00041)

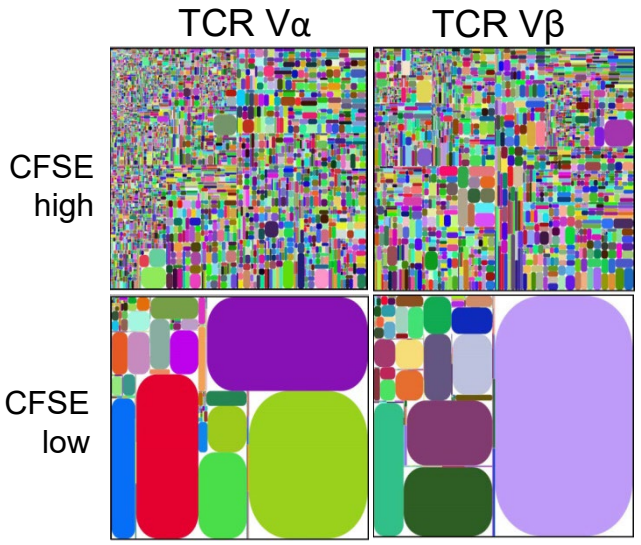


Repertoire data for TCR Vα and Vβ is shown as Tree plots where each spot denotes a TCR and the spot size denotes frequency

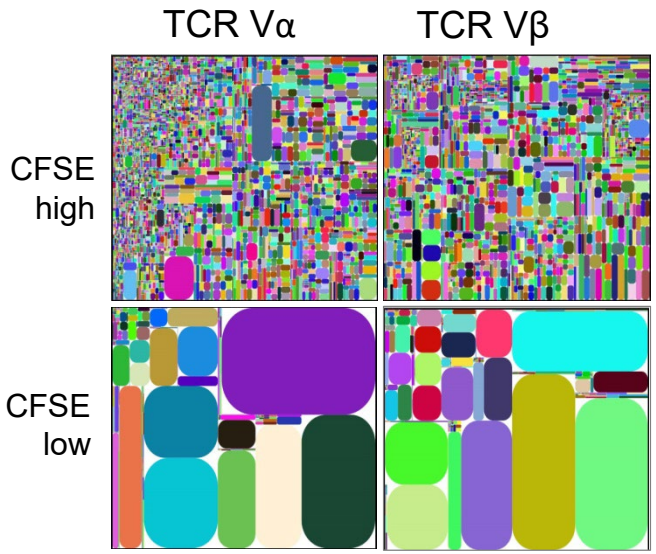
T CELL REPERTOIRE TO MODI-2 EPITOPES IN HUMANS

RESPONSES IN HEALTHY DONORS TO HOMOCITRULLINATED PEPTIDES

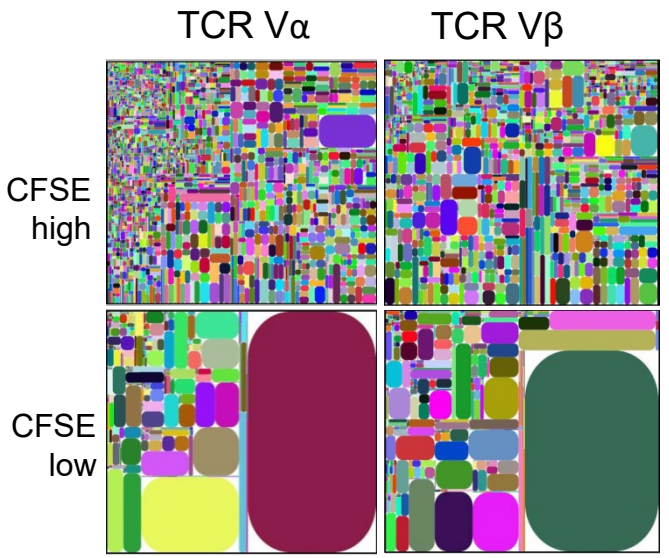
Aldo 74Hcit (BD0016)



Aldo 140Hcit (BD0016)

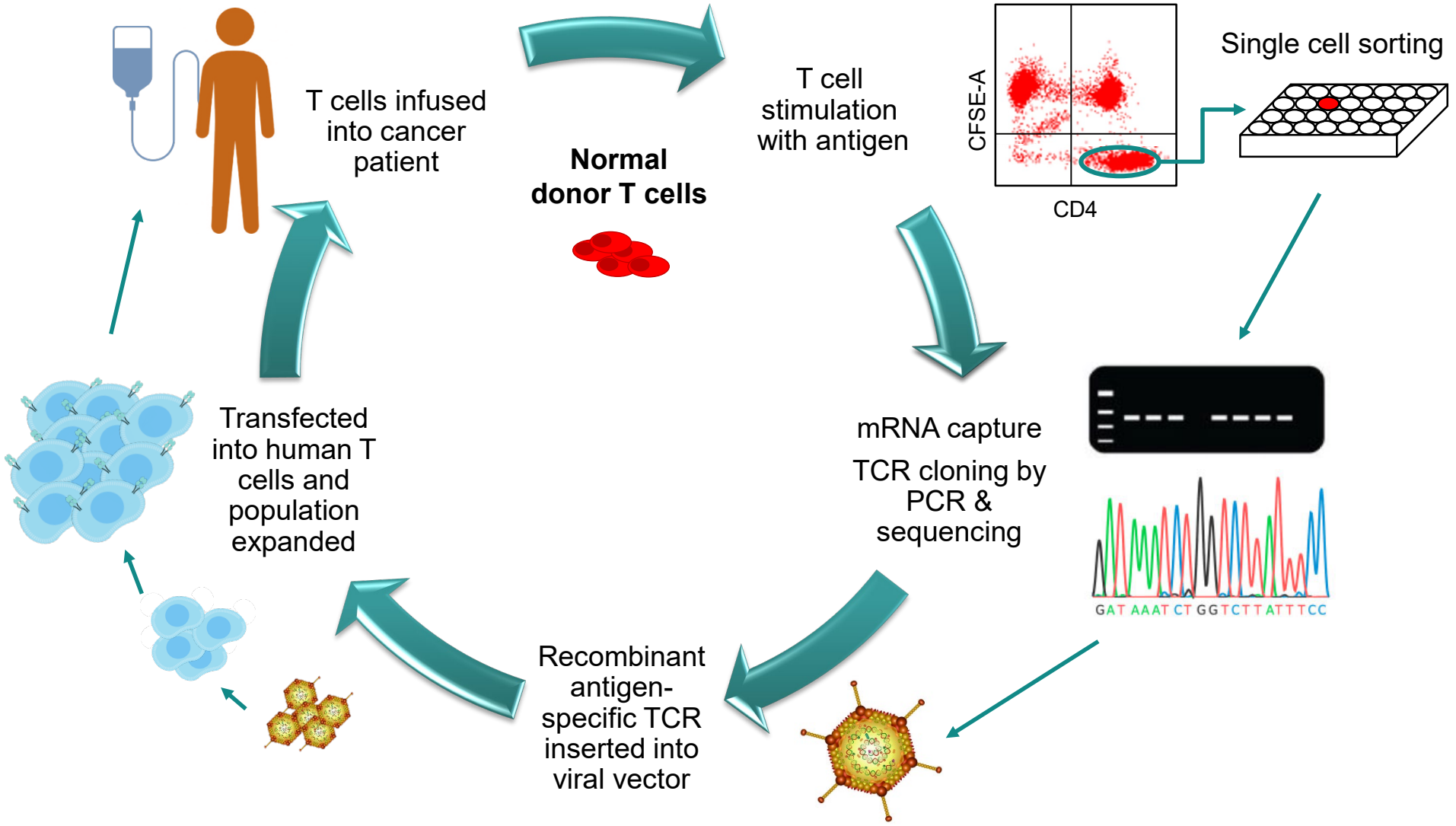


Vim116Hcit (BD0016)

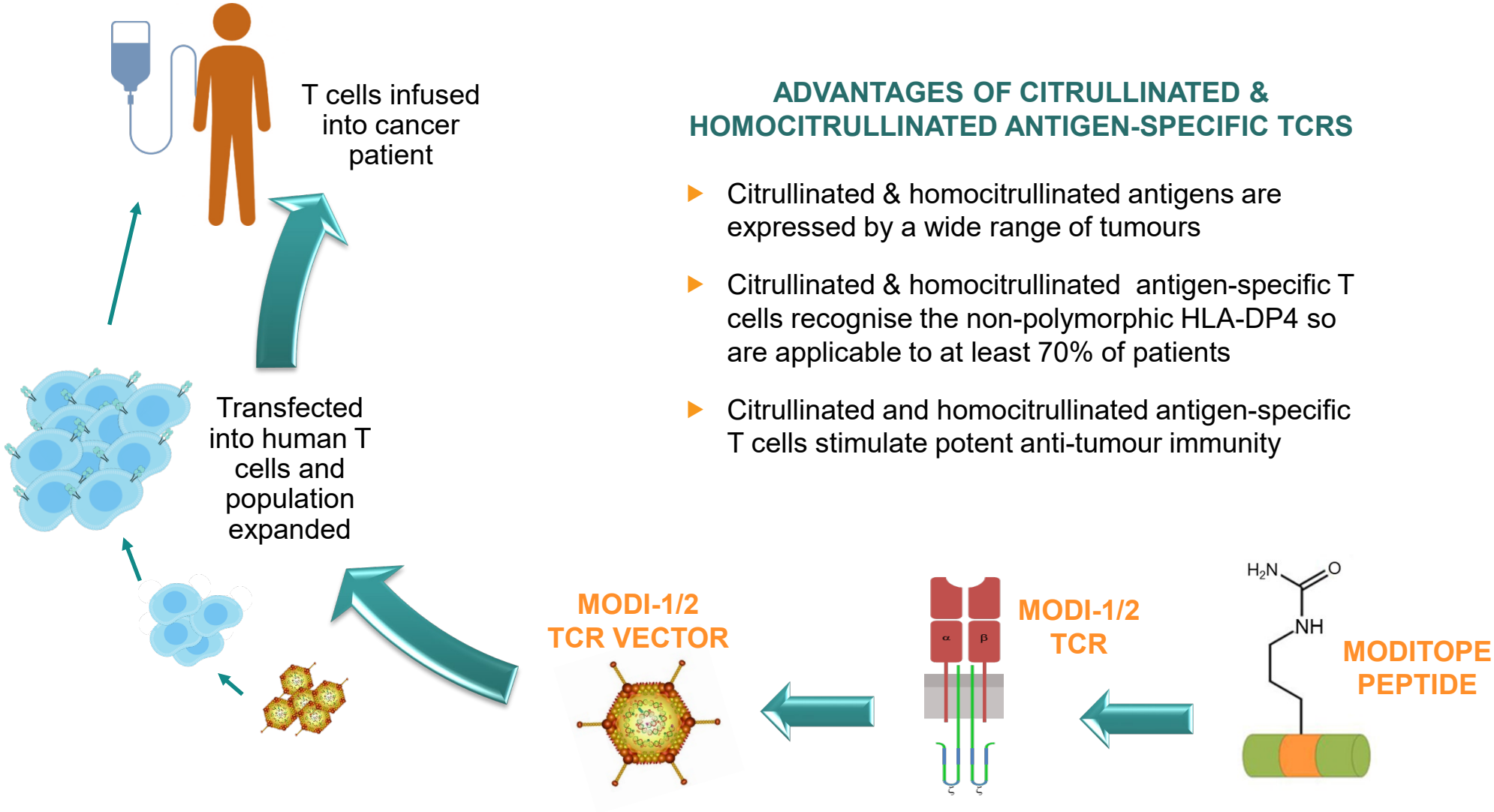


Repertoire data for TCR Vα and Vβ is shown as Tree plots where each spot denotes a TCR and the spot size denotes frequency

TCR TRANSDUCTION AND ADOPTIVE T CELL TRANSFER



MODITOPE® TCR APPROACH



ADVANTAGES OF CITRULLINATED & HOMOCITRULLINATED ANTIGEN-SPECIFIC TCRS

- Citrullinated & homocitrullinated antigens are expressed by a wide range of tumours
- Citrullinated & homocitrullinated antigen-specific T cells recognise the non-polymorphic HLA-DP4 so are applicable to at least 70% of patients
- Citrullinated and homocitrullinated antigen-specific T cells stimulate potent anti-tumour immunity